XomeDx® Slice – Congenital Ichthyosis

PANEL GENE LIST

ABCA12, ABHD5, ALDH3A2, ALOX12B, ALOXE3, AP1S1, ARSE, CASP14, CDSN, CERS3, CHST8, CLDN1, CSTA, CYP4F22, EBP, ELOVL4, FLG, FLG2, GJB2, GJB3, GJB4, GJB6, KDSR, KRT1, KRT10, KRT2, KRT9, LIPN, LOR, MBTPS2, NIPAL4, NSDHL, PEX7, PHGDH, PHYH, PNPLA1, POMP, PSAT1, SDR9C7, SERPINB8, SLC27A4, SNAP29, SPINK5, ST14, STS, TGM1, TGM5, VPS33B, ZMPSTE24

Clinical Features and Genetics

Congenital ichthyoses are a heterogeneous group of disorders manifesting at birth or infancy with visible scaling and/or thickening of the skin, which may be accompanied by variable degree of redness (erythema), skin fragility or blistering, and abnormalities of the hair, nails, or mucous membranes. Scaling and/or thickening of the outermost layer of the skin (so-called hyperkeratosis) may be generalized or localized, may involve other organ systems (syndromic ichthyosis), or may be limited to skin and skin appendages (non-syndromic ichthyosis). The major types of ichthyoses are: (i) epidermolytic ichthyosis (EI) inherited in an autosomal dominant manner, (ii) autosomal recessive (non-syndromic) congenital ichthyosis (ARCI), (iii) various syndromic forms of autosomal recessive congenital ichthyosis, (iv) X-linked ichthyosis (steroid sulfatase deficiency) and related disorders of cholesterol metabolism, (v) autosomal semi-dominant ichthyosis vulgaris, and (vi) various other related genodermatoses or disorders of cornification with hyperkeratosis or peeling (rather than scaling) of the skin.

i. Epidermolytic ichthyoses (EI)

EI presents at birth with erythroderma, blisters or erosions, and larger areas of denuded skin. While skin fragility decreases with age, severe hyperkeratosis with a verrucous, ridged, or cobblestone surface develops over time. Palms and soles may be severely involved or completely spared. There is also a mosaic form of the disease due to somatic variants occurring during embryonic development, with skin findings often following the lines of Blaschko. A mild variant of EI with superficially peeling or denuded areas described as 'molting' or 'Mauserung' is known as superficial epidermolytic ichthyosis (SEI). EI is caused by heterozygous variants in the genes encoding keratin 1 or 10 (*KRT1, KRT10*), while SEI is due to variants in keratin 2 (*KRT2*). A type of EI limited to palms and soles (so-called epidermolytic palmoplantar keratoderma) is caused by variants in the *KRT9* gene. This group of disorders is inherited in an autosomal dominant pattern, in which about 50% of variants occur sporadically (*de novo*).

ii. Autosomal recessive (non-syndromic) congenital ichthyosis (ARCI)

Most neonates with ARCI present as collodion babies with a taut translucent membrane encasing the entire body that lasts for up to two weeks. In severe cases, ectropion, eclabium, and scarring alopecia of the scalp and eyebrows may be present. After shedding the collodion membrane, the presentation and severity of ARCI between individuals can vary significantly. At one end of the spectrum is severe 'classic' lamellar ichthyosis (LI), which is characterized by large, dark brown, plate-like scale without underlying erythroderma. At the other end is severe 'classic' congenital ichthyosiform erythroderma (CIE) with fine whitish scale and intense redness (erythroderma) of the skin. The clinical features of CIE can be milder than in LI and demonstrate a greater variability in the intensity of redness, scale, and involvement of palms and

soles. However, CIE may cause substantial metabolic stress in young children as well as growth delay. There are also cases of almost complete resolution of the skin disorder, so-called 'self-improving collodion ichthyosis'. The most severe and life-threatening form of ARCI is Harlequin ichthyosis. Infants are usually born prematurely encased in a thick, hard, armor-like covering with deep fissures that severely restricts movements. The tautness of skin results in ectropion, eclabium, malformation of the nose and ear cartilage, alopecia, microcephaly, and swelling of the hands and feet. The postnatal period is usually complicated by respiratory distress, dehydration, electrolyte imbalance, temperature instability, feeding problems, and bacterial infections, often with fatal consequences. Survivors develop clinical features of severe CIE or LI. Most individuals with LI, and the majority of individuals with ARCI overall, have biallelic variants in the transglutaminase-1 gene (*TGM1*). The remainder of individuals with ARCI have biallelic variants in genes involved in the fatty acid and triglyceride metabolism or lipid transport of the skin, including *ABCA12, ALOX12B, ALOXE3, CERS3, CYP4F22, LIPN, NIPAL4,* and *PNPLA1*.

iii. Syndromic forms of autosomal recessive congenital ichthyosis

The skin manifestations of many syndromic forms of ichthyosis can be indistinguishable from those of nonsyndromic forms. Nevertheless, individuals develop progressive signs of involvement of the central and peripheral nervous system (Sjogren-Larsson syndrome; Chanarin-Dorfman syndrome; ichthyosis, spastic quadriplegia, and mental retardation syndrome; Refsum disease; Neu-Laxova syndrome), liver (Chanarin-Dorfman syndrome; MEDNIK syndrome), kidneys (arthrogryposis-renal dysfunction-cholestasis syndrome), eyes (Sjogren-Larsson syndrome; Refsum disease; CEDNIK syndrome; Chanarin-Dorfman syndrome), hearing (Chanarin-Dorfman syndrome), and/or other organs. In Netherton syndrome (NTS), individuals have generalized erythema and superficial peeling or scaling associated with hair shaft abnormalities ("bamboo hair"), allergies, and highly elevated serum levels of immunoglobulin E. In severe cases, failure to thrive, growth retardation, and immune defects resulting in serious recurrent infections may complicate NTS. Neonates with ichthyosis prematurity syndrome (IPS) are born prematurely due to polyhydramnios, and present at birth with thick, caseous, desquamating skin. Life-threatening complications such as asphyxia and respiratory complications may occur in the perinatal period, while skin findings later transition to a mild form of generalized ichthyosis with severe pruritus and other signs of atopic diathesis. The vast majority of these autosomal recessive disorders are caused by deficiency in lipid transport or secretion, or other impairments of the normal lipid composition of the epidermis.

iv. X-linked ichthyosis (steroid sulfatase deficiency) and related disorders of cholesterol metabolism

This X-linked recessive disorder almost exclusively affects males. It is caused predominantly by a deletion of the *STS* gene locus on the short arm of the X-chromosome, resulting in steroid sulfatase deficiency and disturbed cholesterol metabolism. Males with ichthyosis present within the first weeks of life with mild erythroderma and generalized peeling or exfoliation of large translucent scales, which transitions into large, polygonal, tightly adhering, and dark-brown scale symmetrically distributed over the extremities, trunk, and neck. The neck is almost invariably involved, while palms, soles, and face are characteristically spared. Asymptomatic corneal opacities occur in 10-50% of affected males and in some female carriers. Cryptorchidism, hypogonadism, and increased risk for developing testicular cancer are rare.
X-linked recessive chondrodysplasia punctata (CDPX1) is characterized by abnormal cartilage and bone development, hypoplasia of distal phalanges (brachytelephalangy), stippled epiphyses on X-ray (chondrodysplasia punctata) especially in the hands and feet, hearing loss, and short stature. Typical for X-

linked dominant chondrodysplasia punctata (CDPX2) are linear or whorl-like hyperkeratoses, atrophy and pigmentary changes of the skin, coarse alopecia, cataracts, and skeletal abnormalities including short stature, rhizomelic shortening of the limbs, epiphyseal stippling, and craniofacial defects. CDPX1 and CDPX2 are caused by pathogenic variants in the *ARSE* and *EBP* genes, respectively, which both encode proteins critical for normal cholesterol metabolism.

v. Autosomal semi-dominant ichthyosis and ichthyosis vulgaris

Ichthyosis vulgaris (IV) is the most common type of ichthyosis. The disorder initially presents during infancy or early childhood with dry skin and mild to moderate scaling of the extremities with sparing of the groin and flexural areas. In more severe disease, scaling extends to large areas of the trunk, scalp, forehead, and cheeks, and there may be itchiness and heat intolerance. IV is frequently associated with keratosis pilaris and features of atopic disease, such as atopic dermatitis, asthma, and hay fever. IV is inherited as an autosomal semi-dominant disorder, with more subtle features in heterozygotes (penetrance up to 90%), and severe disease with complete penetrance in individuals who are homozygous or compound heterozygous for *FLG* pathogenic variants.

vi. Various other related genodermatoses or disorders of cornification with hyperkeratosis or peeling (rather than scaling) of the skin

Autosomal dominant variants in various connexin genes have been observed in patients with localized hyperkeratosis and erythema. Variants in *GJB2* (connexin 26) and very rarely *GJB6* (connexin 30) are associated with sensorineural hearing loss and a diffuse, honeycomb hyperkeratosis of the palms and soles, with or without development of digital constricting bands, knuckle pads, and leukonychia (white nails). In contrast, variants in the loricrin gene (*LOR*), which is a crucial protein during keratinocyte differentiation, lead to similar skin findings without hearing loss. KID syndrome is the most severe connexin disorder with susceptibility to mucocutaneous infections that can be fatal in the neonatal period, increased risk for squamous cell carcinoma, photophobia, and progressive keratitis leading to vision impairment or blindness. Variants in *GJB3* and *GJB4* (connexin 31 and 30.3) cause erythrokeratodermia variabilis, which presents in infancy with transient erythematous patches that remain for minutes to hours or longer. In addition, hyperkeratosis develops, which can be either generalized or localized and fixed. Both erythema and hyperkeratotic plaques have sharply demarcated edges, and palmoplantar keratoderma is not uncommon. Peeling skin syndrome (PSS) is a rare autosomal recessive genodermatosis characterized by spontaneous peeling of the epidermis, which can be localized or generalized, pruritic or nonpruritic, noninflammatory (type A) or inflammatory (type B), and may include erythema. Presentation of PSS varies from congenital through adult onset with variable severity and may involve different areas of the body. PSS exhibits genetic heterogeneity and can be caused by multiple different genes including *CDSN*, *TGM5* (acral PSS), *CHST8, CSTA, SERPINB8,* and *FLG2*. Histology differs by gene, but often shows separation of the epidermis between the stratum granulosum and the statum corneum.

TEST METHODS

Genomic DNA from the submitted specimen is enriched for the complete coding regions and splice site junctions for most genes of the human genome using a proprietary capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled

and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. Data are filtered and analyzed to identify sequence variants and most deletions and duplications involving three or more coding exons. Smaller deletions or duplications may not be reliably identified. Reported clinically significant variants are confirmed by an appropriate orthogonal method. For the FLG and FLG2 genes, only loss-of-function variants are reported. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Reportable variants include pathogenic variants, likely pathogenic variants, and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported. Please note that while *XomeDx*® Slice – Congenital Ichthyosis captures and sequences the whole exome, analysis is targeted to the limited and specific phenotype-driven gene list for ichthyosis or related disorders.

TEST SENSITIVITY

The clinical sensitivity of the *XomeDx*® Slice – Congenital Ichthyosis test depends in part on the patient's clinical phenotype. Specific information about the diagnostic yield for each gene in selected populations is summarized in the table below. The technical sensitivity of the sequencing test is estimated to be greater than 99%. All genes have 99-100% coverage with a depth of 10 or more reads, with the exceptions of KRT9 and POMP, which have a mean coverage of approximately 94%. Note that small sections of a few individual genes (e.g., keratin genes and *FLG*/*FLG2*) have inherent sequence properties that yield suboptimal data and variants in those regions may not be identified reliably.

Gene	Disorder	Inheritance	Clinical Sensitivity
ABCA12	Harlequin ichthyosis (HI); autosomal recessive congenital ichthyosis (ARCI)	Autosomal Recessive	>93% harlequin ichthyosis; 5-7% of all ARCI[1]
ABHD5	Chanarin-Dorfman syndrome (CDS)	Autosomal Recessive	>95% of CDS[2,3,4]
ALDH3A2	Sjogren-Larsson syndrome (SLS)	Autosomal Recessive	~100% of SLS[5]
ALOX12B	Autosomal recessive congenital ichthyosis (ARCI)	Autosomal Recessive	7-13% of all ARCI[1]
ALOXE3	Autosomal recessive congenital ichthyosis (ARCI)	Autosomal Recessive	4-8% of all ARCI[1]
AP1S1	Mental retardation, enteropathy, deafness, peripheral neuropathy, ichthyosis, and keratoderma (MEDNIK) syndrome	Autosomal Recessive	Rare[6,7]
ARSE	Chondrodysplasia punctata 1 (CDPX1)	X-linked Recessive	60-75% of males with CDPX1; slightly lower in affected females; Deletions occur in 10% of cases[8]
CASP14	Ichthyosis	Autosomal Recessive	Rare[1]
CDSN	Peeling skin syndrome (PSS)	Autosomal Recessive	Rare[9,10]

Gene	Disorder	Inheritance	Clinical Sensitivity
CERS3	Autosomal recessive congenital ichthyosis (ARCI)	Autosomal Recessive	Rare, may be part of a rare contiguous gene deletion syndrome including *CERS3* and *ADAMTS17*[1]
CHST8	Peeling skin syndrome (PSS)	Autosomal Recessive	Rare[11]
CLDN1	Neonatal ichthyosisscleroSing cholangitis (NISCH) syndrome	Autosomal Recessive	Rare[12,13]
CSTA	Peeling skin syndrome (PSS)	Autosomal Recessive	Rare[14,15]
CYP4F22	Autosomal recessive congenital ichthyosis (ARCI)	Autosomal Recessive	3-8% of all ARCI[1]
EBP	Chondrodysplasia punctata 2 (CDPX2)	X-linked Dominant	85% of females with suspected CDPX2 and 91% in females with abnormal sterol profile[16]
ELOVL4	Ichthyosis, intellectual disability, and spastic quadriplegia	Autosomal Recessive	Rare[17,18]
FLG	Ichthyosis vulgaris (IV)	Autosomal Semi-Dominant	~100% of IV[19]
FLG2	Peeling skin syndrome (PSS)	Autosomal Recessive	Rare[20,21,22]
GJB2	Keratitis-ichthyosisdeafness (KID) syndrome; palmoplantar keratoderma with sensorineural hearing loss (PPK/SNHL)	Autosomal Dominant	Nearly 100% of KID syndrome; sensitivity for PPK/SNHL is unknown[23,24]
GJB3	Erythrokeratoderma variabilis (EKV)	Autosomal Dominant / Autosomal Recessive (rare)	38% of EKV[25]
GJB4	Erythrokeratoderma variabilis (EKV)	Autosomal Dominant / Autosomal Recessive (rare)	28% of EKV[25]
GJB6	Clouston syndrome; Keratitis-ichthyosisdeafness (KID syndrome)	Autosomal Dominant	~100% of Clouston syndrome[26]; very rare in KID syndrome[24]
KDSR	Progressive symmetric erythrokeratoderma; harlequin ichthyosis/keratoderma & thrombocytopenia	Autosomal Recessive	Rare[27,28]
KRT1	Epidermolytic ichthyosis (EI); palmoplantar keratoderma (PPK)	Autosomal Dominant	~32% of EI[29]

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Gene	Disorder	Inheritance	Clinical Sensitivity
KRT10	Epidermolytic ichthyosis (EI)	Autosomal Dominant / Autosomal Recessive (rare)	~68% of EI[29]
KRT2	Superficial epidermolytic ichthyosis (SEI)	Autosomal Dominant	Rare, ~100% of SEI[30]
KRT9	Epidermolytic palmoplantar keratoderma (EPPK)	Autosomal Dominant	Rare[31, 32]
LIPN	Autosomal recessive congenital ichthyosis (ARCI)	Autosomal Recessive	Rare[33]
LOR	Loricrin keratoderma	Autosomal Dominant	Rare[34,35]
MBTPS2	Ichthyosis follicularis, alopecia, & photophobia (IFAP) syndrome; Olmsted syndrome	X-linked Recessive	Rare[36,37]
NIPAL4	Autosomal recessive congenital ichthyosis (ARCI)	Autosomal Recessive	5-16% of all ARCI[1]
NSDHL	Congenital hemidysplasia with ichthyosiform nevus and limb defects (CHILD) syndrome	X-linked Dominant	~100% of CHILD syndrome[38]
PEX7	Refsum disease	Autosomal Recessive	<10% of Refsum disease[39]
PHGDH	Neu-Laxova syndrome	Autosomal Recessive	Rare[40,41]
PHYH	Refsum disease	Autosomal Recessive	>90% of Refsum disease[39]
PNPLA1	Autosomal recessive congenital ichthyosis (ARCI)	Autosomal Recessive	Up to 3% of all ARCI[1]
POMP	Keratosis linearis with ichthyosis congenita and sclerosing keratoderma (KLICK) syndrome	Autosomal Recessive	Rare[42,43]
PSAT1	Neu-Laxova syndrome (PSS)	Autosomal Recessive	Rare[41,44]
SDR9C7	Autosomal recessive congenital ichthyosis (ARCI)	Autosomal Recessive	Rare[1]
SERPINB8	Peeling skin syndrome (PSS)	Autosomal Recessive	Rare[45]
SLC27A4	Ichthyosis prematurity syndrome (IPS)	Autosomal Recessive	~100% of IPS[46]; 4% of all ARCI[1]
SNAP29	Cerebral dysgenesis, neuropathy, ichthyosis, and palmoplantar keratoderma (CEDNIK) syndrome	Autosomal Recessive	Rare[47,48]
SPINK5	Netherton syndrome	Autosomal Recessive	66-88% of Netherton syndrome[49,50]
ST14	Autosomal recessive congenital ichthyosis with hypotrichosis	Autosomal Recessive	Rare[51, 52]

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Gene	Disorder	Inheritance	Clinical Sensitivity
STS	Steroid sulfatase deficiency	X-linked Recessive	~85-90% of pts with X-linked ichthyosis have a genomic deletion including STS gene and flanking sequences; the remainder have mutations identifiable by sequencing[53,54]
TGM1	Lamellar ichthyosis (LI); autosomal recessive congenital ichthyosis (ARCI)	Autosomal Recessive	70-90% of LI; 32-68% of all ARCI[1]
TGM5	Acral peeling skin syndrome	Autosomal Recessive	Rare[55,56]
VPS33B	Arthrogryposis- renal dysfunction-cholestasis (ARC) syndrome	Autosomal Recessive	80% of ARC syndrome[57]
ZMPSTE24	Restrictive dermopathy	Autosomal Recessive	Rare[58]

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